II

# THE ROUTINE TREATMENT OF EARLY SYPHILIS

Comments by Col. L. W. HARRISON, D.S.O., M.B., Ch.B., F.R.C.P.E., on a paper by Dr. David Watson.*

THE working Editor of this journal roused the sleeping occupant of the other editorial chair (myself) for assent to the publication of Dr. Watson's article.† Whereupon, after voting for its publication, I temporarily vacated my editorial position and offered him the following, partly as a reply to Dr. Watson's strictures on my practice and teaching and partly to draw attention to some recent work which may prove helpful in the solution of the problem of salvarsan poisoning.

Dr. Watson describes my teaching on the treatment of early syphilis as dangerous and erroneous. Dangerous is a relative term which could even be applied to Dr. Watson's treatment, since under the mild dosage of "914" that he recommends, I have seen such untoward effects as dermatitis and jaundice, while deaths are not unknown after even two small doses of "914." The real question is whether or not the risks of the treatment which I advocate outweigh the advantage of complete eradication of the disease in practically every case of early syphilis which it is designed to secure. As to the risks, I can say only that, if the toxic effects of the treatment practised in my clinic had been serious in even a small proportion of the many thousands of patients to whom it has been administered, the total trouble arising from this cause would very quickly have led to a modification. On the other hand, one may reasonably ask if anyone is justified in avoiding a risk of mild immediate toxic effects in a small proportion of cases by methods which entail the greater risks attendant on non-eradication of the disease, with its late effects on the patient and

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† The Junior Editor (E. R. T. C.) offers his apologies to his Senior Colleague for having aroused him from his well-earned slumber, whilst recuperating from and preparing for (*inter alia*) his Editorial activities.

its probable transmission to others. Dr. Watson urges that these risks are non-attendant on his methods of treatment, and takes me to task for scorning the treatment by the feeble course of " 914 " in conjunction with Hyd. c Cret. by mouth, followed by administration of the same mercurial preparation for two years which is unfortunately still practised by many in this country. I have always been puzzled to understand how mercury in fine sub-division is absorbed from the bowel, and could not find any explanation in S. Lomholt's exhaustive article on mercury in Jadassohn's *Handbuch der Haut-u. Geschlechtskrankheiten*, Vol. XVIII., where he concludes his discussion of the subject with the statement that in practice one now scarcely ever uses metallic mercury in the treatment of syphilis by mouth, but rather the mercuric and mercurous salts. Perhaps, however, the explanation lies in a recent note by the Pharmacy Sub-Committee of the Pharmacopœia Commission to the effect that some experiments have shown that Hyd. c. Cret. made according to the formula of the present Pharmacopœia rapidly develops considerable quantities of soluble mercury chloride on keeping. If this is so, a patient under treatment by Hyd. c. Cret. depends for his cure on mercury perchloride in a dosage which depends on the staleness or otherwise of the Hyd. c. Cret. at the time he swallows it. My views on this form of treatment are based on my experience of the late effects of syphilis in patients who have undergone it. Dr. Watson advances results of his own which he claims as evidence of its good effects. Here he goes much further than I have ever ventured, since I have presented my results only as evidence of what " can be reasonably expected from various forms of treatment as regards the proportion of failures " (M.R.C. Special Report Series, No. 132, p. 4). One may reasonably ask if Dr. Watson's claim for the form of treatment which he advocates is justified by his evidence. This is presented in two tables, the first showing results of blood tests after the first course of treatment, and the second, results of tests of patients under treatment for two years or more, these tests having apparently been made whilst the patients were actually under treatment, or only immediately after its suspension ; at any rate, no mention is made of any period of observation after suspension of treatment. I doubt if anyone of experience

in the critical evaluation of scientific evidence would judge that these tables warrant Dr. Watson's claims for the treatment to which they refer, and we are left with the conclusion that his choice of method is based upon subjective " impression " of experience rather than upon critical study of collected objective results. As, in the earlier part of his paper, Dr. Watson has referred to some results of tests after the first course of treatment which I have published, I hasten to say that his and mine are not comparable. His primary and secondary cases may, for anything we know, have contained a large proportion of initially sero-negative primary cases, whereas those of mine which he has quoted were all initially sero-positive. The results are further not comparable, because the Wassermann tests were not necessarily of equal delicacy. Assuming that the method by which his specimens were tested was quite specific in the sense of not affording falsely positive reactions, I could predict with a fair degree of confidence that in a comparison on the same sera it would not prove to be more delicate than the method by which mine were tested, and it might prove much less so. I have seen a large number of methods in this country compared on the same sera with mine, and in every instance where a given method afforded more positive reactions in syphilis cases, it has also given one or more non-specific reactions; as a matter of fact, the great majority of the other methods with which it has been compared on the same sera have proved far less delicate and therefore more likely to make the clinicians whose specimens are tested by them satisfied with the effects of their first course of treatment. Referring to my statement that the most that mercury continued for two years is likely to do is to keep the serum reactions negative, and everybody concerned in a fool's paradise, Dr. Watson asks if it really matters, once the reactions are negative, whether they are kept so by mercury or " 914." I ought perhaps to have said that the most it is likely to do is to keep the serum reactions negative *whilst it is being administered*, and that disappointment in the form of a reversion to positive very quickly after its suspension is likely to ensue in too high a proportion of cases, as I know from experience. In this connection the results which Dr. Watson shows in the faithful fifty who continued under his observation

for two years or more do not promise well for the future when the treatment has been stopped ; what of the multitude who did not continue taking Hyd. c Cret. over a period of two years, or, if they did, forgot to take it for days or weeks together ? If the patient is injected with a suitable bismuth or mercury compound, one has at least an assurance that the remedy circulates in his blood stream rather than in his intestines, or, without the intervention of these, in the town's sewage system.

Whilst, however, disagreeing with Dr. Watson's method of avoiding toxic effects, believing that it is short-sighted and purchased at the cost of efficiency, I agree heartily that we should concentrate on methods of making treatment as free as possible from toxic effects, and in this connection would like to draw attention to some recent publications which offer hope of helping us considerably. A. Savulesco recently advocated the solution of each dose of " 914 " in 5 c.c. of a 20 per cent. solution of sodium dehydrocholate. The bile salt is believed to tone the liver and protect it against the effect of the arsenobenzene compound. So much so that the author states that, as a matter of routine, he gives a course of from 5·0 to 6·0 gm. " 914 " in the space of two to three weeks without ill-effect, the individual doses being from 0·75 to 0·9 gm. given every two to five days. My experience of the use of sodium dehydrocholate as a solvent of " 914 " and as a remedy for arsenobenzene jaundice is so far limited, but is promising.

In the same connection, the views of various workers on a dependence of arsenobenzene dermatoses on hepatic insufficiency are interesting. B. Spiethoff has reported excellent results in severe salvarsan dermatitis of men and in salvarsan intoxications of animals from the administration of liver extract in the form of Hepatrat. This is given either by mouth or by intramuscular injection of a preparation made for him by Nordmark-Werke, Hamburg. The parenteral route is employed for those who cannot tolerate Hepatrat by mouth, or do not seem to be absorbing it, and the dose of 5 c.c., containing 100 liver units, is given at least three times a week. W. Milbrandt quotes the views of E. Hoffmann, Heinrichsdorff, Schiff and others that salvarsan dermatitis is due to liver disturbance, and reports the results of animal experiments which support this theory. He also

repeated the results obtained by Spiethoff, and showed also that in animals sensitised by intradermal injection of salvarsan the sensitiveness was reduced very considerably by the use of Hepatrat. Animals which had become marasmic under chronic poisoning with salvarsan were rapidly restored to health by the same means. H. N. Cole and colleagues in a recent paper on " Toxic Effects following Use of the Arsphenamines " also stated they had had good results from the use of liver extract in dermatitis.

Another communication deserves wide notice, as it teaches that we have been on entirely wrong lines in stressing a preponderance of carbohydrates in our patients' diet, and rather that we should limit them, advocating particularly a diet that is rich in fats and proteins. E. B. Craven, Jr., refers to the advocacy, by many workers, of a diet rich in carbohydrates which is based on the investigations of Davis and Whipple in 1919 into the influence of fasting and various diets on liver injury effected by chloroform, and says: " To us it did not seem necessarily to follow that the efficacy of a high carbohydrate diet in preventing liver injury from chloroform poisoning would hold for a drug so chemically dissimilar as arsphenamine, even though the type of liver injury, namely, central necrosis, is the same in both."

Accordingly he fed different series of dogs on diets as follows :—

" (1) The carbohydrate diet consisted of boiled rice liberally sprinkled with sugar and made into a paste by the addition of skim milk. The rice was rolled into balls and covered with cracker meal."

" (2) The fat diet consisted of either beef or pork fat, or both, with the addition of small quantities of lean beef. It was found necessary to add this lean meat because the dogs would not eat fat alone. In such a mixture the fat by weight always amounted to 70 to 75 per cent. of the total."

" (3) The protein diet was made up of lean beef without any bones and with a negligible quantity of fat."

" (4) Water was supplied *ad libitum*."

In four series of experiments on thirty dogs, ten each on a high carbohydrate, a high fat and a high protein

TABLE I

| "COH" Dogs. | | "Fat" Dogs. | | "Protein" Dogs. | | "Starvation" Dogs. | | |
|---|---|---|---|---|---|---|---|---|
| Jaundice. | Necrosis. | Jaundice. | Necrosis. | Jaundice. | Necrosis. | Jaundice. | Necrosis. | |
| + | Marked | o | o | — | — | — | — | 0·02 gram per kilo, 2 doses. |
| +* | Extreme | o | o | — | — | — | — | |
| + | Marked | o | o | o | o | — | — | 0·02 gram per kilo, 3 doses. |
| + | Moderate | o | o | o | o | — | — | |
| + | Marked | +o | Very slight | o | o | — | — | |
| +* | Extreme* | o | o | o | Slight | — | — | 0·03 gram per kilo, 2 doses. |
| + | Moderate | +o | o | o | Slight | — | — | |
| + | Marked | o | o | o | Slight | — | — | |
| + | Extreme | o | o | o | o | — | — | 0·03 gram per kilo, 1 dose. |
| + | Extreme | + | Extreme | o | Moderate | — | — | |
| — | — | — | — | o | Moderate | — | — | |
| — | — | — | — | o | Moderate | — | — | |
| — | — | — | — | o | o | + | Extreme | 0·03 gram per kilo, 1 dose. |
| — | — | — | — | o | o | + | Extreme | |

* Jaundice after first dose.

diet, and all receiving exactly equal amounts of arsphenamine based on the body weight, the results were as shown in Table I.

Referring to the dog on a fat diet which exhibited extreme necrosis, he considers it probable that the injury here was due to starvation. In this connection he mentions that occasionally a dog would not eat the diet. Whenever possible in such cases the dog was removed and another substituted, but in one case an animal which had refused food for two days was injected with arsphenamine. " He promptly became jaundiced and at the autopsy showed extensive liver damage." " To test the hypothesis that starvation was the predisposing factor here, a small series of four dogs was used. Two of these animals were starved for forty-eight hours (water *ad lib.*). The other two were fed a meat diet. Arsphenamine was then given in a dosage of 0·03 gram per kilo of body-weight. On the following day, both of the starvation animals were very sick. They had vomited repeatedly, were very weak and listless, and were jaundiced. All four animals were sacrificed. The two ' starvation ' animals showed extreme liver necrosis. The two ' protein ' dogs showed no liver damage."

On the strength of Voegtlin's observation that glutathione reduces the toxic effect of " arsenoxide " on rats, Craven tried the effect of Cystine, which contains the same SH. radicle; but in ten dogs fed on carbohydrates it failed, since in these, as in ten others on carbohydrates without Cystine each injected with 0·03 gm. " 606 " per kilogram, the liver necrosis was equally extensive. Craven's conclusions on his experiments are as follows :—

" (1) High fat and high protein diets provide the maximum protection against the liver injury caused by arsphenamine. Of these two diets, the former is more efficacious."

" (2) High carbohydrate diets afford maximum susceptibility to the liver injury caused by arsphenamine."

" (3) Starvation is important as a predisposing factor toward the liver injury caused by arsphenamine."

" (4) Cystine added to the diet or given intravenously does not increase the protective action of carbohydrate diets."

These experiments may explain much that is perplexing regarding the differing incidence of jaundice in

different groups of patients on approximately the same dosage of "914." In my experience, and that of many colleagues whom I have questioned, jaundice is practically unknown amongst private patients, who are presumably better fed than clinic patients, and probably consume more fat in the form of butter, cream, etc. Often enough it appears in small outbreaks, as in those of acute yellow atrophy which occurred in some military hospitals in the period April, 1917, to April, 1918, and it may be that the additional factor which many have thought necessary to the production of salvarsan jaundice was an insufficient intake of fat, whether through fasting or through deficiency of fat in an otherwise full diet.

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